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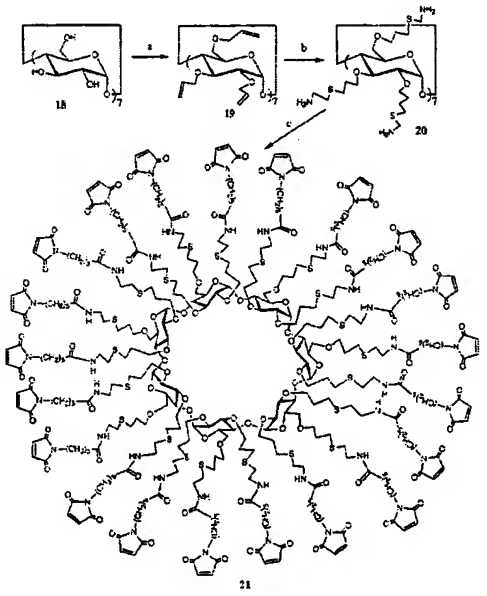
(54) Title: SCAFFOLDED MALEIMIDE CLUSTERS FOR MULTIVALENT PEPTIDE ASSEMBLY



(57) Abstract: Disclosed are scaffolded maleimide clusters, methods of making said clusters and use of said clusters as templates for multivalent peptide assembly. Multiple maleimide functionalities were introduced onto a scaffold molecule by the reaction of a core-centered polyamines with methoxycarbonylmaleimide or with activated esters of maleimide-containing compounds. The scaffolded maleimides allow rapid, highly chemoselective, and high-yield ligation with thiolcontaining peptides under virtually neutral conditions at room temperature. The disclosed mild and highly efficient ligation method is extremely valuable for synthesizing large and complex multivalent peptides that may not be easily obtained by conventional ligation methods. These novel scaffolded maleimide clusters allow a highly chemoselective ligation with a thiolcontaining peptide under virtually neutral conditions, providing a new and efficient approach for multivalent peptide assembly. The disclosed mild and highly efficient ligation method is extremely valuable for synthesizing large and complex multivalent peptides that may not be easily obtained by conventional ligation methods. A series of multivalent peptides containing the sequence of the 36-mer HIV-1 inhibitor DP178 (T20), the T-helper epitope from tetanus toxoid (830-844), and the minimum epitope sequence of the potent HIV-neutralizing antibody 2F5 were synthesized. Carbohydrates and cholic acid were chosen as the scaffold because of their rigidity and mufti-functionality. Thus, the topology of the multivalent peptides can be controlled by the defined spatial orientation of the maleimide functionalities on the rigid scaffold core. The resulting multivalent gp41 peptides incorporating strands of DP178 on the monosaccharide and the cholic acid templates were found to be able to form three or four a-helix bundles. Moreover, the multivalent peptides containing strands of the long gp41 peptide DP178 were highly immunogenic and were able to raise high titers of peptide-specific antibodies, in the absence of any additional adjuvant. Therefore, these and related multivalent peptides constructed on the maleimide clusters may be used as novel immunogens, potential inhibitors, protein mimics, artificial proteins, and powerful antigens for a broad range of biomedical applications.

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